(54) Title: METHOD AND DEVICE FOR MEASURING ACCESS FLOW
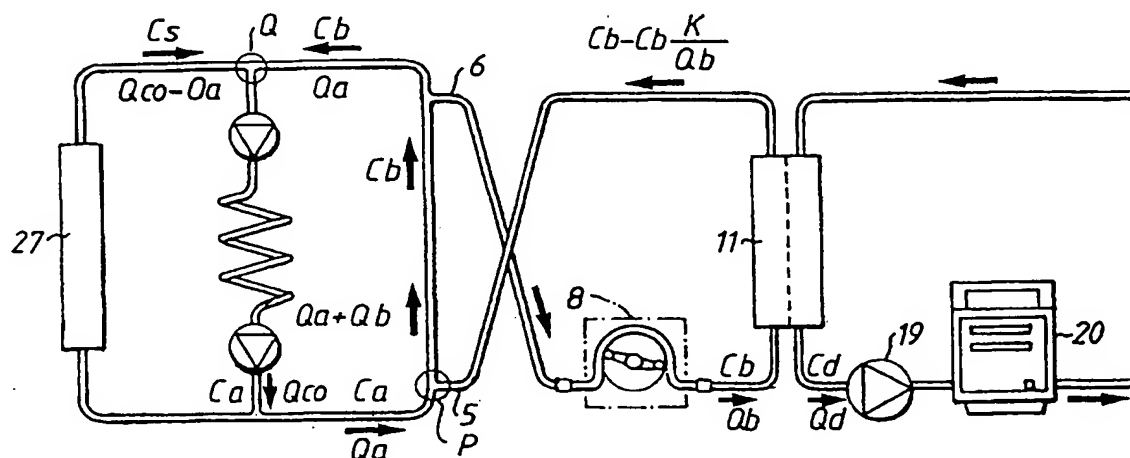
(57) Abstract

An arterial needle removes blood from the access to an extracorporeal circuit comprising a dialyzer and a venous needle returns the blood to the access site. Blood passes along one side of the membrane of the dialyzer and dialysis fluid along the other side. The concentration (Cd norm and Cd rev) of urea in the dialysate emitted from the dialyzer is measured with the needles in the normal position and in a reversed position. The access flow rate before the arterial needle is calculated according to the formula: Cd norm / Cd rev = 1 + Keff/Qa in which Keff is the effective clearance of the dialyzer and Qa is the access flow rate.

Method and device for measuring access flow

AREA OF INVENTION

The present invention relates to a method and device for measuring blood flow rate in a blood access. Blood is taken out from the body of a mammal to an extracorporeal blood circuit through a blood access, via needles or a catheter.

PRIOR ART

There are several types of treatments in which blood is taken out in an extracorporeal blood circuit. Such treatments involve, for example, hemodialysis, hemofiltration, hemodiafiltration, plasmapheresis, blood component separation, blood oxygenation, etc. Normally, blood is removed from a blood vessel at an access site and returned to the same blood vessel or at another location in the body.

In hemodialysis and similar treatments, an access site is commonly surgically created in the nature of a fistula. Blood needles are inserted in the area of the fistula. Blood is taken out from the fistula via an arterial needle and blood is returned to the fistula via a venous needle.

A common method of generating a permanent access site having capability of providing a high blood flow and being operative during several years and even tens of years, is the provision of an arterio-venous fistula. It is produced by operatively connecting the radial artery to the cephalic vein at the level of the forearm. The venous limb of the fistula thickens during the course of several months, permitting repeated insertion of dialysis needles.

An alternative to the arterio-venous fistula is the arterio-venous graft, in which a connection is generated from,

for example, the radial artery at the wrist to the basilic vein. The connection is made with a tube graft made from autogenous saphenous vein or from polytetrafluorethylene (PTFE, Teflon). The needles are inserted in the graft.

A third method for blood access is to use a silicon, dual-lumen catheter surgically implanted into one of the large veins.

Further methods find use in specific situations, like a no-needle arterio-venous graft consisting of a T-tube linked to a standard PTFE graft. The T-tube is implanted in the skin. Vascular access is obtained either by unscrewing a plastic plug or by puncturing a septum of said T-tube with a needle. Other methods are also known.

During hemodialysis, it is desirable to obtain a constant blood flow rate of 150 - 500 ml/min or even higher, and the access site must be prepared for delivering such flow rates. The blood flow in an AV fistula is often 800 ml/min or larger, permitting delivery of a blood flow rate in the desired range.

In the absence of a sufficient forward blood flow, the extracorporeal circuit blood pump will take up some of the already treated blood entering the fistula via the venous needle, so called access or fistula recirculation, leading to poor treatment results.

The most common cause of poor flow with AV fistulas is partial obstruction of the venous limb due to fibrosis secondary to multiple venipunctures. Moreover, stenosis causes a reduction of access flow.

When there is a problem with access flow, it has been found that access flow rate often exhibit a long plateau time period with reduced but sufficient access flow, followed by a short period of a few weeks with markedly reduced access flow leading to recirculation and ultimately access failure. By constantly monitoring the evolution of the access flow during consecutive treatment sessions, it is possible to detect imminent access flow problems.

Several methods have been suggested for monitoring recirculation and access flow. Many of these methods involve injection of a marker substance in blood, and the resultant

recirculation is detected. The methods normally involve
measurement of a property in the extracorporeal blood circuit.
Examples of such methods can be found in US 5,685,989,
US 5,595,182, US 5,453,576, US 5,510,716, US 5,510,717,
5   US 5,312,550, etc.

Such methods have the disadvantage that they cannot detect
when the access flow has decreased to such an extent that
recirculation is at risk, but only when recirculation prevails.
Moreover, it is a drawback that injection of a substance is
10   necessary.

A noninvasive technique that allows imaging of flow
through AV grafts is color Doppler ultrasound. However, this
technique requires expensive equipment.

The measurement of access flow rate necessitates the
15   reversal of the flows in the extracorporeal circuit. A valve
for such reversal is shown in i.a. US 5605630 and US 5894011.
However, these valve constructions comprises dead ends in which
blood may stand still for a long time and coagulate, which is a
drawback.

20

DISCLOSURE OF INVENTION

An object of the present invention is to provide a method
and a device for measuring the access flow rate without
interfering with the blood and without injecting a substance in
25   blood.

Another object of the invention is to provide a method and
a device for measuring access flow rate without measuring on
the blood in the extracorporeal blood circuit or in the access
or blood vessel.

30   According to the invention, it is required to reverse the
blood flow through the access. Thus, a further object of the
invention is to provide a valve for reversing the blood flow.

A still further object of the invention is to provide a
method for determining when the blood flow rate is so small
35   that risk for recirculation prevails.

These objects are achieved with a method and an apparatus
for estimating fluid flow rate (Qa) in a fluid flow access,
comprising removing a first fluid flow from said access at a

removal position to an external flow circuit comprising a
dialyzer having a semipermeable membrane, said first fluid flow
passing along said membrane at one side thereof and a dialysis
fluid being emitted from the other side thereof, and returning

5   said first fluid flow from said external flow circuit to said
access at a return position downstream of said removal
position, measuring a first variable which is essentially
proportional to a concentration (Cd norm) of a substance in
said dialysis fluid emitted from the dialyzer, reversing the

10   removal position with the return position and measuring a
second variable which is essentially proportional to the
concentration (Cd rev) of said substance in said dialysis fluid
in the reversed position; and calculating the fluid flow rate
(Qa) in said flow access from said measured concentrations.

15   Preferably, the calculation of the fluid flow rate in said
flow access takes place by calculating the ratio between the
first and the second variable and using the formula:
Cd norm / Cd rev = 1 + K/Qa,   in which Cd norm and Cd rev are
values proportional to the concentrations of said substance in

20   the dialysis fluid in the normal and reversed positions,
respectively, and K is the clearance of the dialyzer and Qa is
the access flow rate.

         The blood flow access may be in a mammal for obtaining
access to a blood vessel, such as a hemodialysis access in the

25   nature of an arterio-venous shunt or fistula. In the latter
case, the dialyzer clearance K is replaced by the effective
dialyzer clearance Keff obtained by taking into account a
cardiopulmonary recirculation and in the normal position.

         The substance is preferably selected from the group of:

30   urea, creatinine, vitamin B12, beta-two-microglobuline and
glucose, or may be an ion selected from the group of: Na^+, Cl^-,
K^+, Mg^{++}, Ca^{++}, HCO_3^-, acetate ion, or any combination thereof
as measured by conductivity; and wherein said concentration is
measured as the concentration difference between the outlet and

35   the inlet of the dialyzer, if applicable.

         It is possible to measure the actual concentration of the
substance. However, since only the ratio between the
concentrations in the normal and the reversed position,

respectively, is needed, it is possible to measure a value
which is proportional to the concentration of said substance,
whereby said value is used in place of said concentration. Said
property may be the blood concentration of said substance in
5   the external circuit, either before or after the dialyzer.
Alternatively, the relative whole body efficiency (K_{wh}/V) may
be used, as explained in more detail below.

The effective clearance Keff may be obtained by the
equation Keff = Qd * Cd / Cs, where Qd is the flow of dialysis
10   fluid emitted from the dialyzer, Cd is the concentration of
said substance in said dialysis fluid and Cs is the
concentration of said substance in systemic venous blood.

A method of measuring the concentration (Cs) of said
substance in systemic venous blood comprises the steps of:
15   stopping the blood flow in the external flow circuit for a time
period sufficient to allow the cardiopulmonary circulation to
equalize; starting the blood flow in the external flow circuit
with a slow speed to fill the arterial line with fresh blood
before the measurement; and measuring the equalized
20   concentration of said substance in the dialysis fluid at a low
dialysate flow rate or at isolated ultrafiltration. It is
advantageous to make the measurement of the effective clearance
at the initiation of the treatment.

The concentration (Cs) of said substance in systemic
25   venous blood may be estimated by: calculating a whole body mass
of urea (Murea) in the body of the patient, estimating or
measuring the distribution volume (V) of urea in the body of
the patient; and estimating the concentration (Cs) of said
substance in the blood by dividing the whole body mass of urea
30   with the distribution volume. In this way, the mean
concentration of urea in the whole body is obtrained. However,
the mean concentration in the whole body is slightly higher
than the urea concentration in the systemic blood, except at
the start of the treatment. Thus, this calculation should
35   preferably be done or be extrapolated to the start of the
treatment.

It is possible to discriminate between the condition when
access or fistula recirculation has developed and not. A method

for that purpose would be: changing the blood flow rate (Qb);
monitoring the concentration of said substance in the dialysate
emitted from the dialyzer; and detecting a possible fistula
recirculation in the normal position by correlating a change in
5   said concentration to said change of the blood flow rate.

Preferably, the blood flow rate is decreased and a
corresponding decrease in the urea concentration is monitored,
and the abscence of such a decrease being indicative of fistula
recirculation.

10

SHORT DESCRIPTION OF DRAWINGS

Further objects, advantages and features of the invention
appears from the following detailed description of the
invention with reference to specific embodiments of the
15   invention shown on the drawings, in which

Fig. 1 is a partially schematic view of a forearm of a
patient provided with an AV fistula.

Fig. 2 is a schematic diagram of an extracorporeal
dialysis circuit.

20   Fig. 3 is a schematic diagram of the blood flow circuit in
a patient and in the attached extracorporeal blood circuit.

Fig. 4 is a schematic diagram similar to Fig. 3, but with
the extracorporeal circuit in an alternative reversed position.

Fig. 5 is a schematic diagram of a blood flow circuit
25   including a switch valve.

Fig. 6 is a diagram of the dialysis fluid urea
concentration versus time, including a portion with reversed
flow access according to the invention.

Fig. 7 is a schematic diagram similar to the diagram of
30   Fig. 5 comprising an alternative valve arrangement.

Fig. 8 is schematic diagram similar to the diagram of Fig.
7 showing the valve arrangement in an idle postion.

Fig. 9 is schematic diagram similar to the diagram of Fig.
7 showing the valve arrangement in a reversed postion.

35   Fig. 10 is a schematic diagram similar to Fig. 5 with the
pump in an alternative position.

Fig. 11 is a diagram showing calculations with relative
whole body efficiency.

Fig. 12 is a cross-sectional view of a valve housing to be used in the schematic diagram of Figs. 5 and 7 to 10.

Figl 13 is a bottom view of a valve member intended to be inserted in the valve housing of Fig. 12.

5   Fig. 14 is a partially schematic plan view of the valve housing of Fig. 12.

DESCRIPTION OF DETAILED EMBODIMENTS OF THE INVENTION

For the purpose of this description, an access site is a
10   site in which a fluid in a tube can be accessed and removed from and/or returned to the tube. The tube may be a blood vessel of a mammal, or any other tube in which a fluid is flowing. The access flow rate is the flow rate of the fluid in the tube or blood vessel immediately upstream of the access
15   site or removal position.

Fig. 1 discloses a forearm 1 of a human patient. The forearm 1 comprises an artery 2, in this case the radial artery, and a vein 3, in this case the cephalic vein. Openings are surgically created in the artery 2 and the vein 3 and the
20   openings are connected to form a fistula 4, in which the arterial blood flow is cross-circuited to the vein. Due to the fistula, the blood flow through the artery and vein is increased and the vein forms an thickened area downstream of the connecting openings. When the fistula has matured after a
25   few months, the vein is thicker and may be punctured repeatedly. Normally, the thickened vein area is called a fistula.

An arterial needle 5 is placed in the fistula, in the enlarged vein close to the connected openings and a venous
30   needle 6 is placed downstream of the arterial needle, normally at least five centimeters downstream thereof.

The needles 5 and 6 are connected to a tube system 7, shown in Fig. 2, forming an extracorporeal circuit comprising a blood pump 8, such as a dialysis circuit. The blood pump
35   propels blood from the blood vessel, through the arterial needle, the extracorporeal circuit, the venous needle and back into the blood vessel.

The extracorporeal blood circuit 7 shown in Fig. 2 further comprises an arterial clamp 9 and a venous clamp 10 for isolating the patient from the extracorporeal circuit should an error occur.

5   Downstream of pump 8 is a dialyzer 11, comprising a blood compartment 12 and a dialysis fluid compartment 13 separated by a semipermeable membrane 14. Further downstream of the dialyzer is a drip chamber 15, separating air from the blood therein.

Blood passes from the arterial needle past the arterial
10   clamp 9 to the blood pump 8. The blood pump drivs the blood through the dialyzer 11 and further via the drip chamber 15 and past the venous clamp 10 back to the patient via the venous needle. The drip chamber may comprise an air detector, adapted to trigger an alarm should the blood emitted from the drip
15   chamber comprise air or air bubbles. The blood circuit may comprise further components, such as pressure sensors etc.

The dialysis fluid compartment 14 of the dialyzer 11 is provided with dialysis fluid via a first pump 16, which obtains dialysis fluid from a source of pure water, normally RO-water,
20   and one or several concentrates of ions, metering pumps 17 and 18 being shown for metering such concentrates. The preparation of dialysis fluid is conventional and is not further described here.

An exchange of substances between the blood and the
25   dialysis fluid takes place in the dialyzer through the semipermeable membrane. Notably, urea is passed from the blood, through the semipermeable membrane and to the dialysis fluid present at the other side of the membrane. The exchange may take place by diffusion under the influence of a concentration
30   gradient, so called hemodialysis, and/or by convection due to a flow of liquid from the blood to the dialysis fluid, so called ultrafiltration, which is an important feature of hemodiafiltration or hemofiltration.

From the dialysis fluid compartment 14 of the dialyzer is
35   emitted a fluid called the dialysate, which is driven by a second pump 19 via a urea monitor 20 to drain. The urea monitor continuously measures the urea concentration in the dialysate emitted from the dialyzer, to provide a dialysate urea

concentration curve during a dialysis treatment. Such urea
concentration curve may be used for several purposes, such as
obtaining a total body urea mass, as described in WO 9855166,
and to obtain a prediction of the whole body dialysis dose Kt/V
5   as also described in said application. The contents of
WO 9855166 is incorporated in the present specification by
reference.

As described above, the present invention provides a
method of non-invasively measuring the access flow in the
10   fistula immediately before the arterial needle, using the urea
monitor and the dialysis circuit as shown in Fig. 2.

By measuring the dialysis urea concentration during normal
dialysis and then reversing the positions of the needles and
measuring the dialysis urea concentration with the needles in
15   the reversed position, it is possible to calculate the blood
flow in the blood access, without the addition of any substance
to blood or the dialysis fluid.

Fig. 3 shows a simplified schematic diagram of the blood
vessel circuit of a patient and a portion of the dialysis
20   circuit according to Fig. 2. The patient blood circuit
comprises the heart, where the right chamber of the heart is
symbolized by an upper pump 21 and the left chamber of the
heart is symbolized by a lower pump 22. The lungs 23 are
located between the upper and lower pump. From the outlet of
25   the left chamber pump 22 of the heart, the blood flow divides
into a first branch 24 leading to the access 25, normally in
the left forearm of the patient, and a second branch 26 leading
to the rest of the body, such as organs, other limbs, head,
etc. symbolized by a block 27. Blood returning from the body
30   from the organs etc., i.e. from block 27, combines with blood
returning from the access and enters the right chamber pump 21.

The cardiac output flow rate is defined as Qco and the
flow rate of the access is defined as Qa, which means that
Qco - Qa enters the block 27. The venous blood returning from
35   block 27 before being mixed with blood from the access, the
systemic venous blood, has a urea concentration of Cs. The
blood leaving the left chamber pump 22 has a urea concentration

of Ca equal to that passing out to the access 25 as well as to
the block 27.

For measuring the access flow rate, it is necessary to
reverse the flow through the arterial and venous needles. One
way of achieving that is to reverse the needles manually.

Alternatively, Fig. 5 shows a valve 28 for performing the
same operation. The arterial needle 5 is connected to an
arterial inlet line 29 of the valve and the venous needle 6 is
connected to a venous inlet line 30 of the valve. The blood
pump is connected to a first outlet line 31 of the valve and
the returning blood from the dialyzer 11 is connected to a
second outlet line 32 of the valve.

The valve comprises a valve housing and a pivotable valve
member 33, which is pivotable from the normal position shown on
the drawing to a reverse position pivoted 90° in relation to
the normal position.

In the normal position shown in Fig. 5, the arterial
needle 5 is connected to the blood pump 8 and the venous needle
6 is connected to the outlet of the dialyzer, via the drip
chamber, see Fig. 2. In the reversed position, the arterial
needle 5 is connected to the outlet of the dialyzer and the
venous needle 6 is connected to the blood pump 8, as required.

An alternative design of the valve arrangement is shown in
Figs. 7, 8 and 9. In the embodiment of Fig. 7, the arterial
line 29 is connected to an enlarged opening 29a and the venous
outlet line 30 is connected to an enlarged opening 30a, the
openings being arranged in the valve housing 28a diametrically
opposite to each other. Two enlarged openings 31a and 32a are
arranged in the valve housing 28a diametrically opposite each
other and displaced 90° in relation to enlarged openings 29a
and 30a. The pivotable valve member 33a is normally arranged as
shown in Fig. 7 and forms a partition dividing the valve
chamber in two semi-circular portions. The valve member has a
width, which is smaller than the peripheral dimension of the
enlarged openings. The valve member is pivotable 90° to a
reverse position, shown in Fig. 9, in which the blood flows
through the arterial and venous needles are reversed.

During its movement from the normal to the reversed
position, the valve member 33a passes through an idle position
shown in Fig. 8, in which all four enlarged openings are
interconnected, because the width of the valve member is
5   smaller than the peripheral dimension of the enlarged openings.
By this idle position, harm to blood cells may be avoided. Such
harm may be caused by high shear stresses which may occur if
the inlet line 31 to the blood pump or the outlet line 32 from
the dialyzer are completely occluded. By means of the idle
10   position, another advantage is obtained, that the blood needles
are not exposed to rapid change of flows, which in some
instances even may result in dislocation of the needles. When
the valve member is moved from the normal position to the idle
position, the flow through the needles change from the normal
15   flow of, for example, 250 ml/min to essentially zero flow. The
valve member may be placed in the idle position for some
seconds. Then, the valve member is moved to the reversed
position, and the flows through the needles is changed from
essentially zero flow to -250 ml/min. In this way, a more
20   gentle switch between normal and reversed flows may be
obtained.

It is noted, that the positions of the openings and the
valve member may be different so that the pivotal movement may
be less than or more than 90°. Moreover, the openings need not
25   be arranged diametrically in order to achieve the desired
operation. Furthermore, the dimensions of the enlarged openings
in relation to the tubes and lines are not in scale, but the
diameter of the enlarged openings is rather of the same
dimension as the tube inner diameter, as appears more clearly
30   below.

It is noted that the valve is constructed to have as few
dead end portions as possible, in which the blood may stand
still and coagulate. From the drawing, it is appreciated that
no portion of the valve has a dead end construction in any
35   position of the valve body.

Furthermore, another schematic diagram incorporating a
valve is shown in Fig. 10. Fig. 10 differs from Fig. 5 inly in
the placement of the pump 8a, which in the embodiment according

to Fig. 10 is placed between the arterial needle 5 and the
valve 28. In this manner, the pressure across the valve body 33
is less compared to the embodiment according to Fig. 5. The
operation is somewhat different. The blood pump is stopped, and
5   the valve is put in the reversed position. Finally, the pump is
started and pumping the blood in the opposite direction by
reversing the rotational direction of the pump.

    In order to ascertain that no air is introduced into the
patient in either position of the valve, it may be advantageous
10   to add an air detector 34 and 35 immediately before each of the
arterial and venous needle, or at least before the arterial
needle. The air detectors trigger an alarm should they measure
air bubbles in the blood given back to the blood vessel.
Normally, the air detector in the drip chamber is sufficient
15   for this purpose.

    The detailed construction of a valve intended to be used
in the present invention, is disclosed in Figs. 12, 13 and 14.
The valve comprises a valve housing 36 comprising two inlet
connectors and two outlet connectors. All four connectors open
20   into cylindrical valve chamber 41, the four openings being
displaced 90° in relation to each other.

    As shown in Fig. 14, the valve comprises a blood inlet
connector 37 connected to the arterial needle 5 and a blood
outlet connector 38 connected to the venous needle 6. The
25   connector portions are arranged as male Luer connectors to be
connected to flexible tubes ending with a female Luer
connector.

    Furthermore, the valve comprises a circuit outlet
connector 39 connected to the blood pump 8 and a circuit inlet
30   connector 40 connected to the dialyzer outlet. The connector
portions 39 and 40 are arranged as female Luer connectors to
mate with male Luer connectors of the circuit.

    As appears from Fig. 12, the cylindrical valve chamber 41
is closed at the bottom. From the top, a valve member 42 may be
35   introduced into the cylindrical valve chamber. The valve member
42 comprises a valve partition 43 as appears from Fig. 13.

    The valve member also comprises an operating wing 44, by
means of which the valve member may be pivoted 90° between a

normal position, in which the valve partition 43 is situated as shown by dotted lines in Fig. 14, and a reversed position. The pivotal movement is limited by a shoulder 45 of the valve member 42, which cooperates with a groove 46 in the valve

5   housing. The shoulder 45 is provided with a protrusion 46a which cooperates with two recesses 47 and 48 in the normal position and reverse position, respectively, to maintain the valve member in either position. The groove 46 may be provided with a third recess (not shown in the drawing) in order to

10   define said idle position. Such a third recess is positioned in the middle between the two recesses 47 and 48.

The valve member and housing are provided with suitable sealings to ensure safe operation. The operation of the valve is evident from the above description.

15   By studying the theoretical dialysate urea concentrations resulting from a given dialyzer clearance K, a given access blood flow Qa and a given blood urea concentration Cs in the systemic venous blood returning from the body, it is found that the effective urea clearance Keff of the dialyzer, taking the

20   cardiopulmonary recirculation into account, is needed for the calculation of access flow. The effective clearance can be measured, for example as described in EP 658 352, the contents of which is incorporated in the present application by reference.

25   Alternatively, the effective clearance can be calculated from simultaneous systemic venous blood Cs and dialysate Cd measurements of urea concentrations, such as by blood samples.

The systemic blood urea concentration Cs may be measured by the so called stop flow - slow flow technique, where the

30   blood flow is substantially stopped for a couple of minutes to allow the cardiopulmonary recirculation to equalize. Thereafter, the pump is run slowly to fill the arterial line with fresh blood before taking the blood sample. The urea concentration in the so obtained blood sample is equal to the

35   urea concentration Cs in the systemic venous blood returning from the body to the heart.

Alternatively to taking a blood sample, the dialysis fluid flow at the other side of the membrane is stopped and the

slowly flowing blood is allowed to equalize with the dialysate at the other side of the membrane, whereupon the urea concentration of the dialysate is measured to obtain the systemic venous blood urea concentration Cs.

A further method to obtain effective clearance is described in WO 9929355. According to the invention described in WO 9929355, the systemic blood concentration Cs is measured before or at the initiation of the treatment, for example by stop flow - slow flow technique with blood sample or equilisation as described above. After obtaining valid dialysate urea concentration vales Cd from a urea monitor connected to the dialysator outlet line, the initial dialysate urea concentration C_{dinit} at the start of the treatment is extrapolated by the dialysate urea curve obtained.

A still further method of obtaining systemic blood urea concentration Cs is to calculate the urea mass M_{wh} in the whole body and extrapolate the urea mass to the start of the treatment. By dividing the whole body urea mass M_{wh} with the distribution volume V, the systemic blood urea concentration Cs at the start of the treatment is obtained.

By dividing the dialysate urea concentration Cd with the systemic blood urea concentration Cs and multiplicating with the dialysate flow rate Qd, the effective clearance Keff is obtained. It is advantageous to measure the effective clearance Keff at the initiation of the treatment.

Furthermore, in the method of the invention, the blood flows in the arterial and venous needles are reversed. The dialysate urea concentrations in the two cases with normal position of the needles and with reverse position of the needles may be calculated as follows, with reference to Figs. 3 and 4.

The blood urea concentration Cs in the venous blood returning from the body is assumed unchanged when the lines are reversed, and the dialyzer clearance K is also assumed unchanged. For simplicity ultrafiltration is assumed to be zero, but it is also possible to handle a nonzero UF.

The following notations are used:

Qco –   Cardiac Output
Qa   –   Access flow
Qb   –   Blood flow in extracorporeal circuit
Qd   –   Dialysate flow
K   –   Dialyzer clearance
Keff –   Effective dialyzer clearance
Cs   –   Blood urea concentration in systemic venous blood
          returning from the body
Ca   –   Blood urea concentration in the access
Cb   –   Blood urea concentration at the dialyzer inlet
Cd   –   Dialysate urea concentration

The definition of clearance is:

$$K = (\text{removed urea}) / C_b = Q_d * C_d / C_b \qquad (1)$$

Consider first the case in which $Q_a > Q_b$ and the needles are in the normal position. In this case $C_b = C_a$.

Removal from blood must equal appearance in the dialysate so that

$$K * C_a = Q_d * C_d \qquad (2)$$

A mass balance for urea at the point V, see Fig. 3, when mixing the venous return blood with the blood from the access gives:

$$C_a * Q_{co} = C_s * (Q_{co} - Q_a) + C_a * (Q_a - K) \qquad (3)$$

Thus, we obtain a relation between C_a and C_s.

By combining equations 2 and 3 we obtain:

$$C_d = (K/Q_d) * C_s / [1 + K/(Q_{co} - Q_a)] \qquad (4)$$

The definition of effective clearance Keff implies that C_s should be used in the denominator instead of C_b as normally used in dialyzer clearance, which means that

$$\text{Keff} = K * (Cb / Cs) = K / [1 + K/(Qco - Qa)] \tag{5}$$

If we now turn to the case with reversed lines, see Fig. 4, we still have that what is removed from the blood must enter the dialysate, so that in this case

$$K * Cb = Qd * Cd \tag{6}$$

The flow in the fistula between the needles will be $Qa + Qb$ and we can calculate the blood urea concentration at the dialyzer inlet from a urea mass balance at the point P where the dialyzed blood enters the access again

$$Cb * (Qb - K) + Ca * Qa = Cb * (Qb + Qa) \tag{7}$$

We also have the mass balance at the point Q where the venous return blood meets the dialyzed blood in the access return flow:

$$Ca * Qco = Cs * (Qco - Qa) + Cb * Qa \tag{8}$$

By eliminating Ca and Cb we get

$$Cd = (K/Qd) * Cs / [1 + (Qco/Qa) * K / (Qco - Qa)] \tag{9}$$

Since Cs, K and Qd in the two cases are unchanged, it is possible to obtain the ratio of dialysate urea concentrations:

$$Cd\ norm / Cd\ rev = 1 + (K/Qa) / [1 + K/(Qco-Qa)] =$$
$$= 1 + Keff/Qa \tag{10}$$

In practice, the two dialysate urea concentrations are probably best found by a curve fit to the dialysate urea curves before and after the switch of lines, with an extrapolation to the time of switching from the respective side, see Fig 6, which shows the urea concentration Cd of the dialysate during a normal hemodialysis treatment.

During a time period of about 10 minutes, marked with a
ring in Fig. 6, the arterial and venous needles are reversed.
After a initial time period for allowing the urea monitor to
measure accurately, the urea concentration with reversed lines
is appr. 0.8 times the original urea concentration, which means
that Cdnorm / Cdrev = 1.25. Thus, if Keff is 200 ml/min, as
measured with the needles in the normal position or estimated
as described above, the access flow is 800 ml/min.

The effective clearance may also be obtained as a rough
estimate from blood and dialyzer flows and dialyzer
characteristics, e.g. from the dialyzer date sheet.

In the present specification, there is used three
different clearances, namely dialyzer clearance, effective
clearance and whole body clearance. If dialyzer clearance is
250 ml/min for a certain blood flow rate and dialysate flow
rate, the effective clearance is normally 5 to 10% lower, such
as 230 ml/min. The whole body clearance is still 5 to 15%
lower, such as 200 ml/min. The dialyzer clearance is the
clearance as measured directly on the dialyzer. The effective
clearance is the clearance also taking into account the cardio-
pumonary recirculation. Finally, the whole body clearance is
the effective clearance further taking into account other
membranes in the body restricting the flow of urea from any
part of the body to the dialyasate. The concept of whole body
clearance is described in WO 9855166, the contents of which is
herewith incorporated by reference.

The effective clearance used in the formula may also be
obtained from a measurement according to the method described
in EP 658 352 mentioned above, with the needles in the normal
position. This will give a measure of the effective plasma
water urea clearance, which then has to be converted to whole
blood clearance. The method of EP 658 352 essentially comprises
that the conductivity of the dialysis fluid upstream of the
dialyzer is increased by for example 10% and then returned to
the original value. The result at the outlet side of the
dialyzer is measured and reults in a measure of the effective
clearance Keff of the dialyzer.

Alternatively, the effective clearance may be calculated according to equation Keff = Qd * Cd / Cs. The systemic venous urea concentration may be measured at the same time as the dialysate urea concentration Cd, or by the methods described above.

Another method would be to use the value of total body urea mass Murea obtained by the method according to WO 9855166, mentioned above. By obtaining the urea distribution volume V by Watson's formula or any other method, the venous urea concentration would be approximately:

$$Cs = Murea / V \tag{11}$$

In the method of WO 9855166, the relative whole body efficiency of the dialyzing process K_{wb}/V is obtained. Note, that whole body clearance is used, as indicated by the subscript wb. According to said WO 9855166, urea concentration is proportional to the relative whole body efficiency according to the formula:

$$K_{wb}/V = (Q_d \cdot c_d) / m \tag{12}$$

Thus, if (K_{wb}/V) is used instead of Cd in the above equation (10), a similar result is obtained, if it is presumed that m is constant, i.e. the measurement must be extrapolated to the same time instance:

$$(K_{wb}/V) \text{ norm} / (K_{wb}/V) \text{ rev} = 1 + Keff/Qa \tag{13}$$

As is mentioned in said WO 9855166, it is possible to calculate the relative whole body efficiency only from dialysate urea measurement. Since we are interested only in the ratio in the normal and reversed position, we do not need to calculate the actual K_{wh}.

Fig. 11 shows a plot of the relative whole body efficiency K/V (min^{-1}). The period with reversed lines is shown inside a circle. In all other respects, the same discussion applies as is given above.

The calculations above assume that the extracorporeal blood flow rate Qb does not exceed the access flow rate Qa. If this is the case there will be access recirculation and the flow in the access will be reversed when the needles are in the
5   normal position. The calculation of dialysate urea concentration is unchanged for the needles in reversed position, but has to be modified for the needles in normal position. Calculations corresponding to those above show that the ratio above between dialysate urea concentrations for
10   normal and reversed needle positions will be:

$$Cd\ norm\ /\ Cd\ rev = 1 + Keff\ /\ Qb \qquad\qquad (14)$$

where Keff is the effective clearance with the effect of
15   recirculation included, that is with the needles in the normal position.

     The only difference is that the calculation will now give the extracorporeal blood flow Qb instead of the access flow. This blood flow is known, so in practice this means that when
20   the result is an access flow rate Qa close to the blood flow rate Qb, recirculation should be suspected, and this always means that the access has to be improved.

     Keff/Qb is a figure lower than one, normally for example 0.6 - 0.9. Keff/ Qa should be considerably lower, for example
25   0.1 - 0.4. Thus, when Cd norm/Cd rev approaches or is lower than a predetermined number, such as 1.2 or 1.5, further calculations should be done for determining if access recirculation is present.

     A simple procedure is to decrease the blood flow Qb
30   somewhat. If the dialysate concentration then decreases, this means that there is no access or fistula recirculation at least at the lower blood flow.

     The above calculations can also be made for the situation where ultrafiltration is present. However, it is a simple
35   measure to reduce the ultrafiltration to zero during the measurement interval. Moreover, the error induced by ultrafiltration is small and may be neglected.

The measurement should be performed during a time
interval, which is considerably larger than 30 seconds so that
cardio-pulmonary recirculation has been developed. The
measurement time for obtaining valid results may be 5 minutes
5   with the needles reversed, while measurements with the needles
in correct position may be done in 5 minutes or continuously
during the treatment.

The method is also applicable to the methods of treatment
comprising infusion of a dialysis solution to the blood before
10   or after the dialyzer, called hemofiltration and
hemodiafiltration. The result is the same as given above.

If the access is a venous catheter, there is no cardio-
pulmonary recirculation and the calculations becomes simpler.
The result is the same, except that the effective clearance
15   Keff is replaced by the dialyzer clearance K, since the
systemic venous urea concentration Cs becomes the same as the
dialyzer inlet urea concentration Cb.

It should be noted that all flow rates, clearances and
urea concentrations in the calculations relate to whole blood.
20   Approximately 93% of plasma is water, depending on the protein
concentration, and about 72% of erythrocytes is water.
Depending on the hematocrit value, the blood water volume is
10 - 13 % lower than the volume of whole blood, see for example
Handbook of Dialysis, Second Edition, John T. Daugirdas and
25   Todd. S Ing, 1994, page 18.

The effective urea clearance obtained according to
EP 658 352 relates to blood water, and must therefore be
increased by 10 - 13 % before being used in the present
formulas. Blood urea concentration values obtained from a
30   laboratory relate in general to plasma, and must therefore be
decreased by about 7% in order to relate to whole blood.

Alternatively, all urea concentrations, flow rates and
clearances may be used as relating to blood water. The
effective clearance is then used unchanged, but the calculated
35   access flow will relate to blood water, and has to be increased
by 10 - 13 % to relate to whole blood.

The invention has been described above with reference to
use in the human body and using urea as a marker for measuring

access flow. However, any other substance present in blood and which can be measured at the dialysate side of the dialyzer may be used according to the invention, such as creatinine, vitamin B12, beta-two-microglobuline, NaCl or any combination of ions. Another alternative is to measure conductivity.

It is also possible to measure a property proportional to the concentration, since it is the ratio that is involved in the equations. Thus, urea concentration may be measured by measuring conductivity differences after passing the urea containing fluid through a urease column, and such conductivity difference can be used directly in place of the concentration values in the equations.

Other indirect methods of measuring any of the above-mentioned substances concentrations may be used as long as the measurements are made at the dialysate side of the dialyzer. Another alternative is to measure the blood urea concentrations by any known method, either before or after the dialyzer, since these concentrations are proportional to the concentrations in the formulas.

The invention has been described above with reference to use in the human body. However, the invention can be used in any tube system where a fluid is passed and a portion thereof is taken out for dialysis, such as in beer or wine production.

CLAIMS

5   1. A method of estimating fluid flow rate (Qa) in a fluid
flow access, comprising:
         removing a first fluid flow from said access at a removal
position to an external flow circuit comprising a dialyzer
having a semipermeable membrane, said first fluid flow passing
10   along said membrane at one side thereof and a dialysis fluid
being emitted from the other side thereof, and returning said
first fluid flow from said external flow circuit to said access
at a return position downstream of said removal position;
         measuring a first variable which is essentially
15   proportional to a concentration (Cd norm) of a substance in
said dialysis fluid emitted from the dialyzer;
         reversing the removal position with the return position
and measuring a second variable which is essentially
proportional to the concentration (Cd rev) of said substance in
20   said dialysis fluid in the reversed position; and
         calculating the fluid flow rate (Qa) in said flow access
from said measured concentrations.
         2. The method of claim 1, wherein calculating the fluid
flow rate in said flow access takes place by the formula:
25

         Cd norm / Cd rev = 1 + K/Qa

in which Cd norm and Cd rev are values proportional to the
concentrations of said substance in the dialysis fluid in the
30   normal and reversed positions, respectively, and K is the
clearance of the dialyzer and Qa is the access flow rate.
         3. The method as claimed in claim 2, wherein said flow
access is a blood flow access in a mammal for obtaining access
to a blood vessel.
35   4. The method as claimed in claim 3, wherein said flow
access is a hemodialysis access in the nature of an arterio-
venous shunt or fistula, and wherein the dialyzer clearance K
is replaced by the effective dialyzer clearance Keff obtained

by taking into account a cardiopulmonary recirculation and in
the normal position.

    5. The method of anyone of the preceding claims, wherein
said substance is selected from the group of: urea, creatinine,
vitamin B12, beta-two-microglobuline and glucose.

    6. The method of anyone of the preceding claims, wherein
said substance is an ion selected from the group of: Na^+, Cl^-,
K^+, Mg^{++}, Ca^{++}, HCO_3^-, acetate ion, or any combination thereof
as measured by conductivity; and said concentration is measured
as the concentration difference between the outlet and the
inlet of the dialyzer.

    7. The method of claim 5 or 6, wherein the measuring step
is performed by measuring a property which is proportional to
the concentration of said substance, whereby said property is
used in place of said concentration.

    8. The method of claim 7, wherein said property is anyone
of: the blood concentration of said substance in the external
circuit; and the relative whole body efficiency (K_{wh}/V).

    9. The method of anyone of claims 3 to 8, wherein said
Keff is obtained by the equation

    $$Keff = Qd * Cd / Cs$$

where Qd is the flow of dialysis fluid emitted from the
dialyzer, Cd is the concentration of said substance in said
dialysis fluid and Cs is the concentration of said substance in
systemic venous blood.

    10. The method of claim 9, wherein the concentration (Cs)
of said substance in systemic venous blood is measured by:

    stopping the blood flow in the external flow circuit for a
time period sufficient to allow the cardiopulmonary circulation
to equalize;

    starting the blood flow in the external flow circuit with
a slow speed to fill the arterial line with fresh blood before
the measurement;

    measuring the equalized concentration of said substance in
the dialysis fluid at a low dialysate flow rate or at isolated
ultrafiltration.

    11. The method of claim 9, wherein the concentration (Cs)
of said substance in systemic venous blood is estimated by:

calculating a whole body mass of urea (Murea) in the body
of the patient,

estimating or measuring the distribution volume (V) of
urea in the body of the patient;

estimating the concentration (Cs) of said substance in the
blood by dividing the whole body mass of urea with the
distribution volume.

12. The method of anyone of the preceding claims, further
comprising:

changing the blood flow rate (Qb);

monitoring the concentration of said substance in the
dialysate emitted from the dialyzer;

detecting a possible fistula recirculation in the normal
position by correlating a change in said concentration to said
change of the blood flow rate.

13. The method of claim 12, wherein the blood flow rate is
decreased and a corresponding decrease in the urea
concentration is monitored, and the abscence of such a decrease
being indicative of fistula recirculation.

14. An apparatus for estimating fluid flow rate (Qa) in a
fluid flow access, comprising:

removal means for removing a first fluid flow from said
access at a removal position to an external flow circuit
comprising a dialyzer having a semipermeable membrane, said
first fluid flow passing along said membrane at one side
thereof and a dialysis fluid being emitted from the other side
thereof;

returning means for returning said first fluid flow from
said external flow circuit to said access at a return position
downstream of said removal position;

measuring means for measuring a first variable which is
essentially proportional to a concentration (Cd norm) of a
substance in said dialysis fluid emitted from the dialyzer;

reversal means for reversing the removal position with the
return position for measuring a second variable which is
essentially proportional to the concentration (Cd rev) of said
substance in said dialysis fluid in the reversed position; and

calculating means for calculating the fluid flow rate (Qa) in said flow access from said measured concentrations.

15. The apparatus of claim 14, wherein the calculating means calculates the fluid flow rate in said flow access by the formula:

$$Cd\ norm\ /\ Cd\ rev = 1 + K/Qa$$

in which Cd norm and Cd rev are values proportional to the concentrations of said substance in the dialysis fluid in the normal and reversed positions, respectively, and K is the clearance of the dialyzer and Qa is the access flow rate.

16. The apparatus as claimed in claim 14 or 15, wherein said flow access is a blood flow access in a mammal for obtaining access to a blood vessel.

17. The apparatus as claimed in claim 16, wherein said flow access is a hemodialysis access in the nature of an arterio-venous shunt or fistula, and wherein the dialyzer clearance K is replaced by the effective dialyzer clearance Keff obtained by taking into account a cardiopulmonary recirculation.

18. The apparatus of anyone of claims 14 to 17, wherein said substance is selected from the group of: urea, creatinine, vitamin B12, beta-two-microglobuline and glucose.

19. The apparatus of anyone of claims 14 to 18, wherein said substance is an ion selected from the group of: Na^+, Cl^-, K^+, Mg^{++}, Ca^{++}, HCO_3^-, acetate ion, or any combination thereof as measured by conductivity; and said concentration is measured as the concentration difference between the outlet and the inlet of the dialyzer.

20. The apparatus of claim 18 or 19, wherein the measuring means is adapted to measure a property which is proportional to the concentration of said substance, whereby said property is used in place of said concentration.

21. The apparatus of claim 20, wherein said property is anyone of: the blood concentration of said substance in the external circuit; and the relative whole body efficiency (K_{wh}/V).

22. The apparatus of anyone of claims 17 to 21, wherein said Keff is obtained by the equation

Keff = Qd * Cd / Cs

where Qd is the flow of dialysis fluid emitted from the
5   dialyzer, Cd is the concentration of said substance in said dialysis fluid and Cs is the concentration of said substance in systemic venous blood.

23. The apparatus of claim 22, further comprising means for measuring the concentration (Cs) of said substance in
10   systemic venous blood, including:

means for stopping the blood flow in the external flow circuit for a time period sufficient to allow the cardiopulmonary circulation to equalize and stopping the flow of dialysis fluid;

15   means for starting the blood flow in the external flow circuit with a slow speed to fill the arterial line with fresh blood before the measurement;

means for measuring the equalized concentration of said substance in the dialysis fluid at a low dialysate flow rate or
20   at isolated ultrafiltration.

24. The apparatus of claim 22, further comprising means for estimating the concentration (Cs) of said substance in systemic venous blood, including:

means for calculating a whole body mass of urea (Murea) in
25   the body of the patient,

means for estimating or measuring the distribution volume (V) of urea in the body of the patient;

means for estimating the concentration (Cs) of said substance in the blood by the formula by dividing the whole
30   body mass of urea with the distribution volume.

25. The apparatus of anyone of claims 14 to 24, further comprising:

means for changing the blood flow rate (Qb);

means for monitoring the concentration of said substance
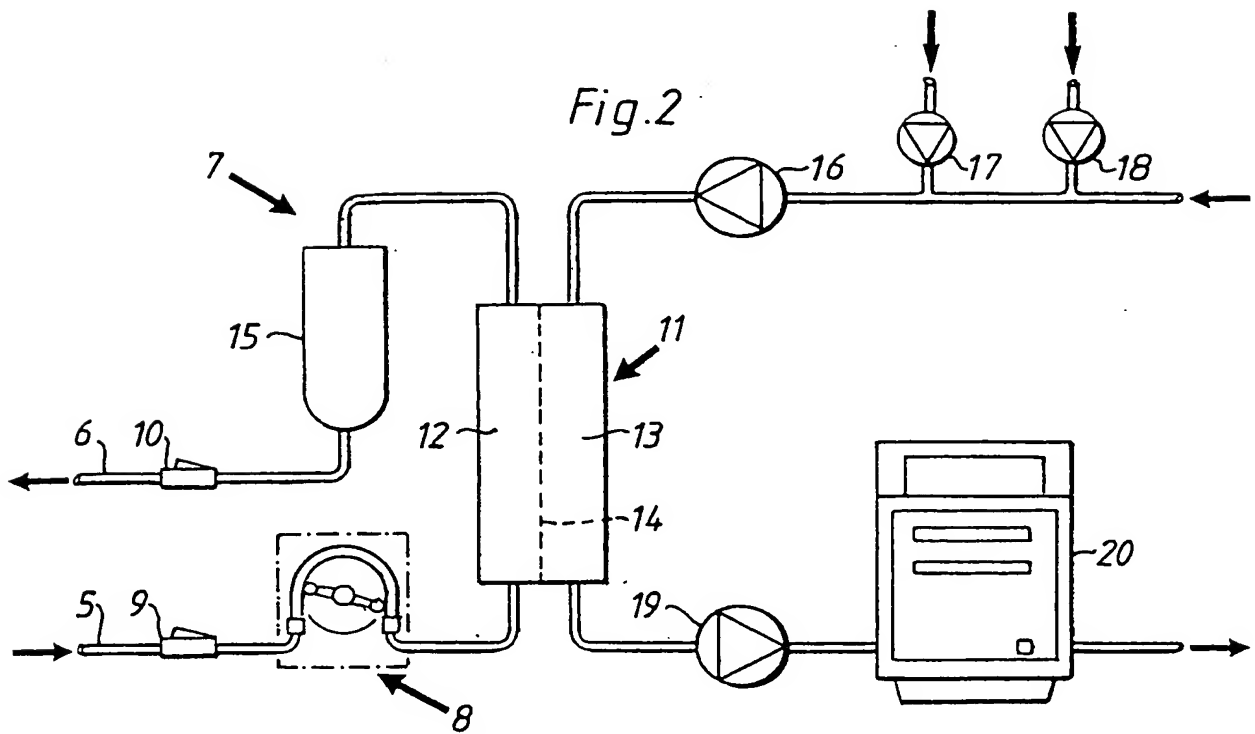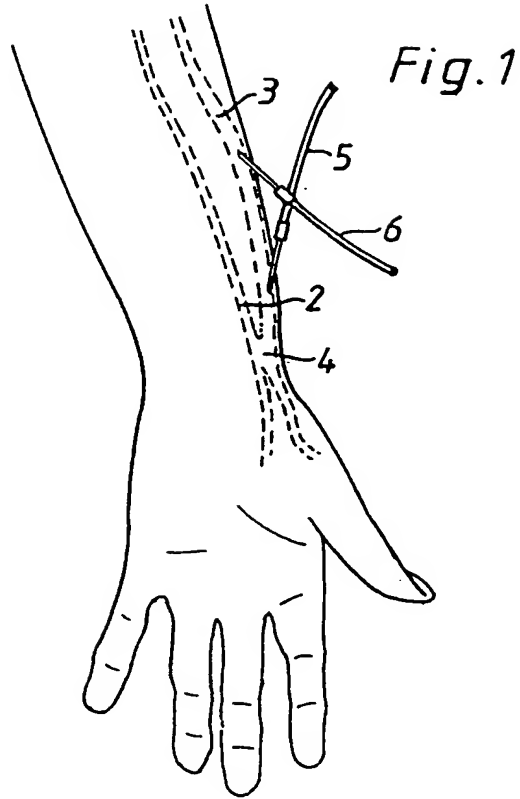35   in the dialysate emitted from the dialyzer;

means for detecting a possible fistula recirculation in the normal position by correlating a change in said concentration to said change of the blood flow rate.

26. The apparatus of claim 25, comprisng means for decreasing the blood flow rate and means for monitoring a corresponding decrease in the urea concentration, whereby the abscence of such a decrease being indicative of fistula recirculation.

27. The apparatus of anyone of claims 14 to 24, wherein said reversal means comprises:

a valve means arranged between the removal means and the dialyzer and between the returning means and the dialyzer for reversing the blood flow direction through the removal means and the returning means, said valve means comprising two inlet and two outlet openings and a valve member, said valve member being arranged to adopt an idle position in which all four inlet and outlet openings are interconnected.

28. The apparatus of claim 27, further comprising an air detector arranged between the valve means and at least one of the arterial needle and the venous needle.
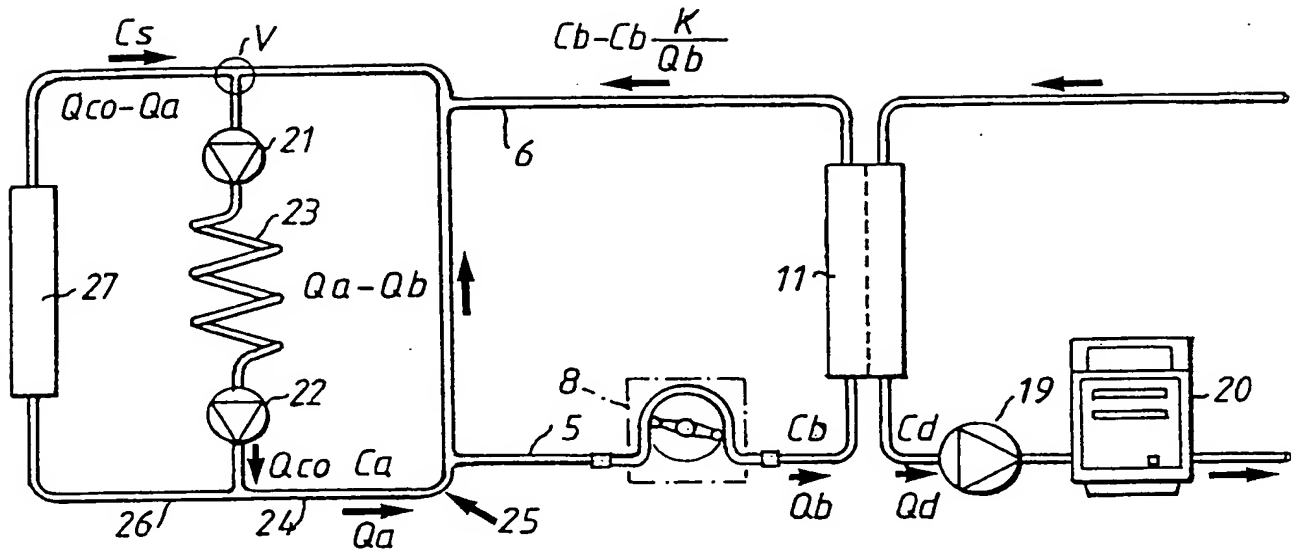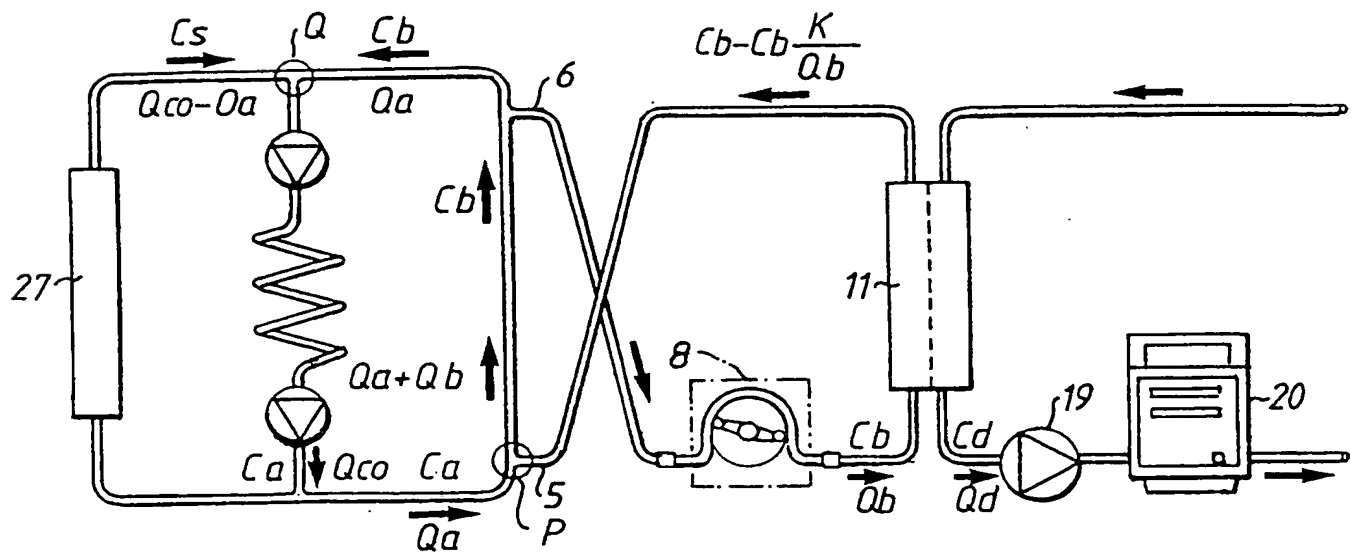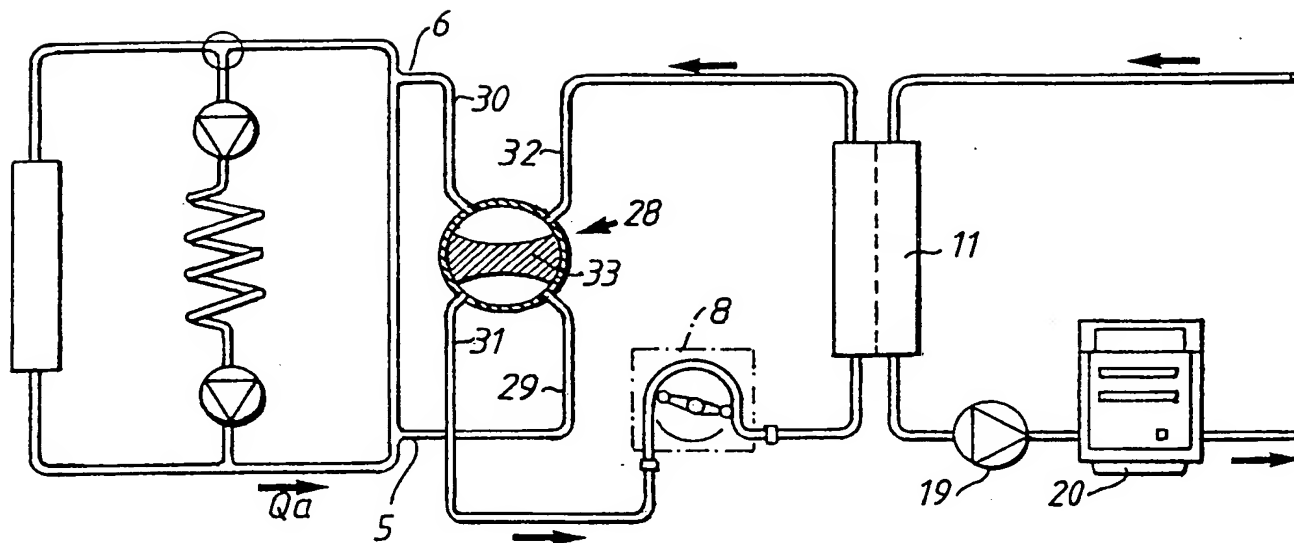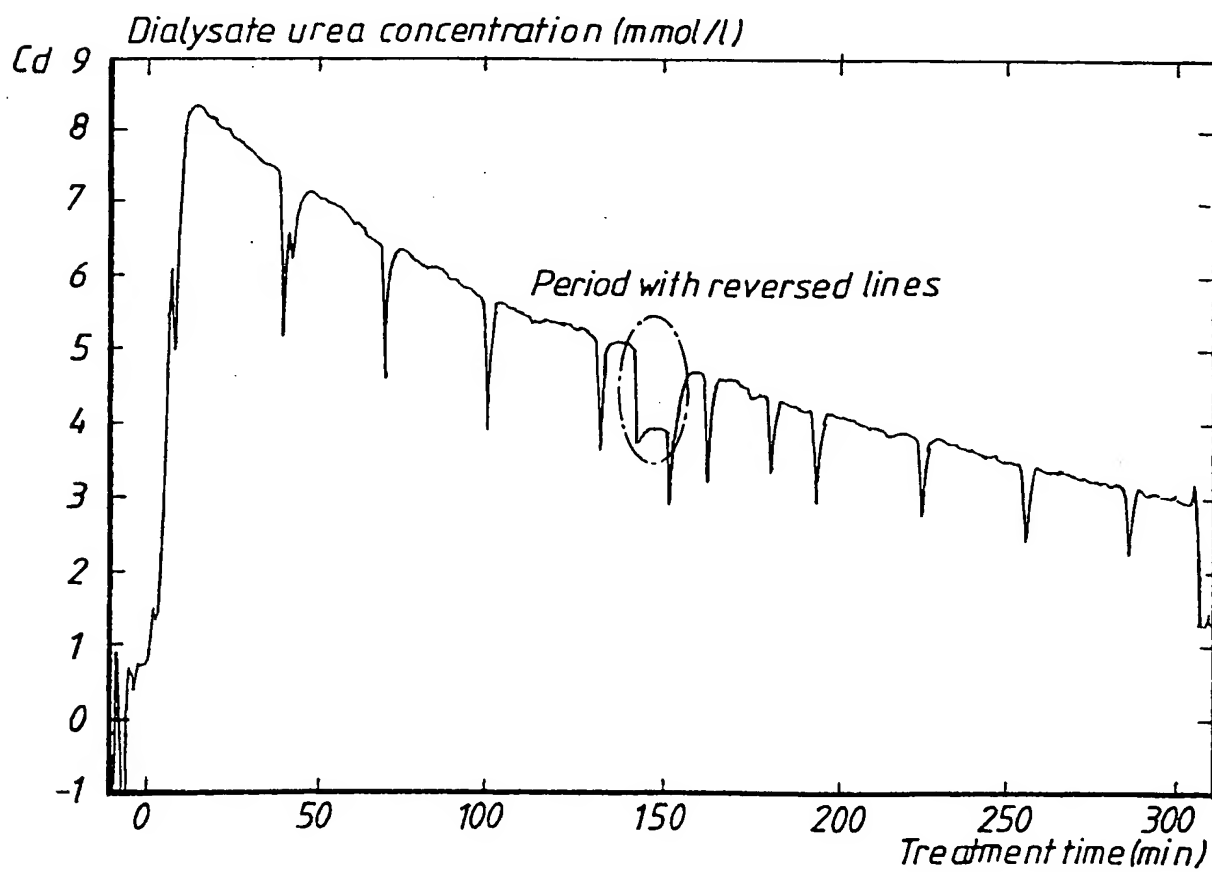
Fig.1

Fig.2

Fig.3

Fig.4

Fig.5

Fig.6

Dialysate urea concentration (mmol/l)

Period with reversed lines
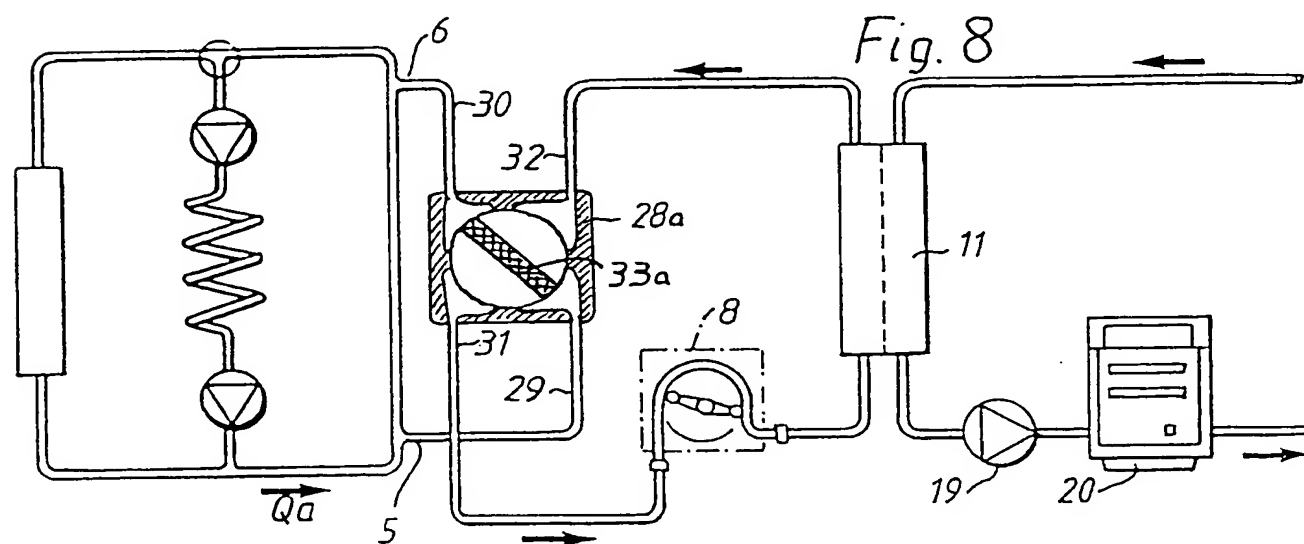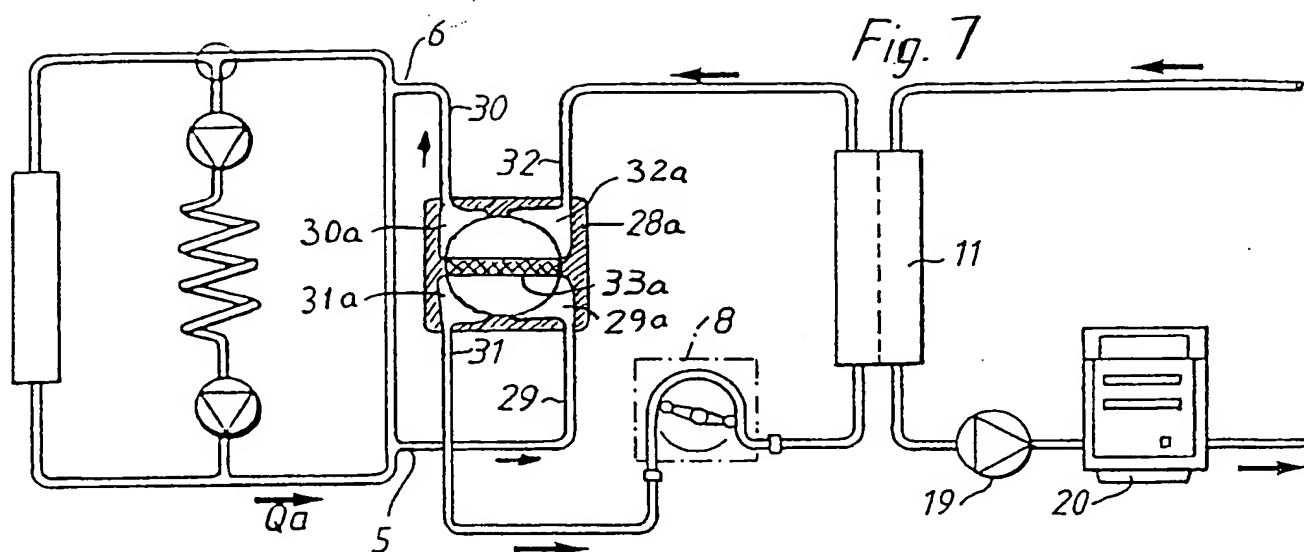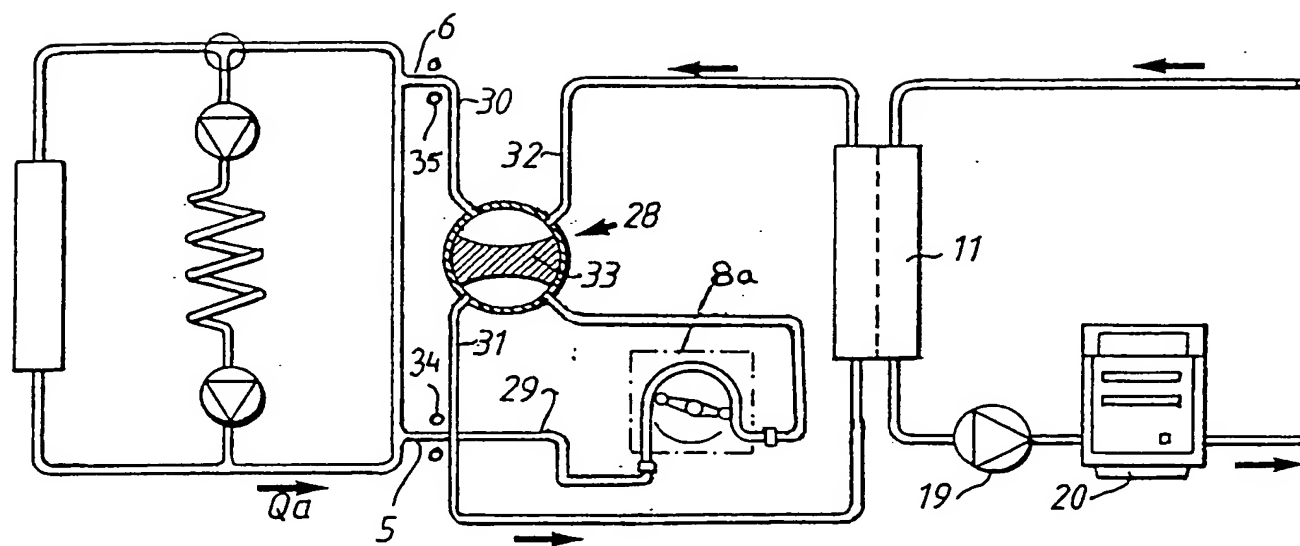
Treatment time (min)

Fig. 7

Fig. 8

Fig. 9
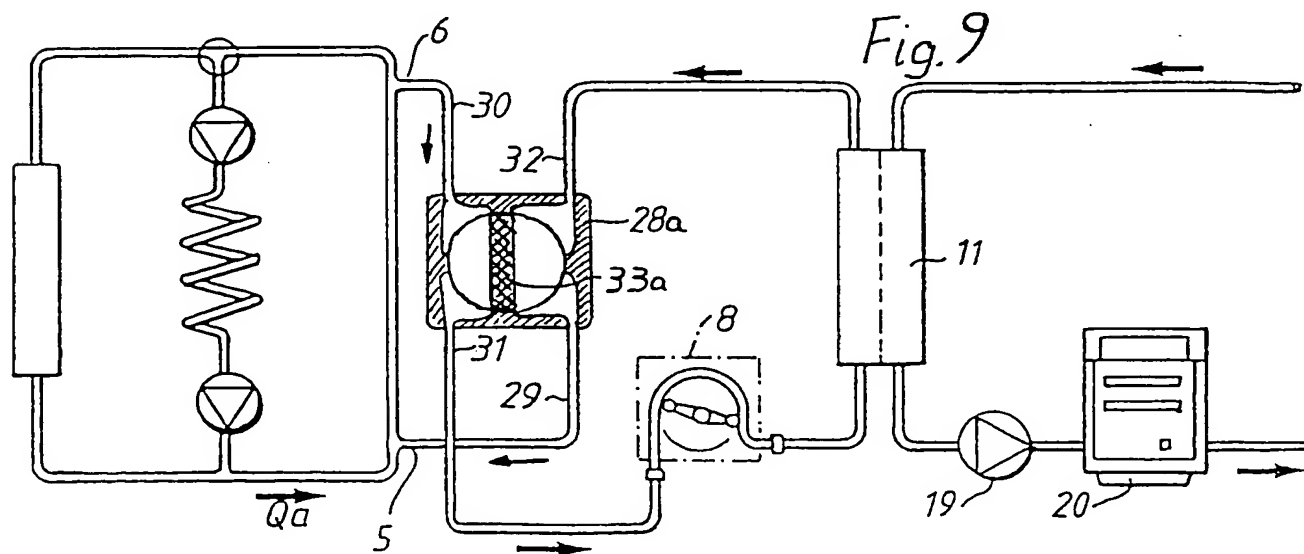
Fig. 10

Fig. 11

Relative whole body efficiency K/V (per min)

Period with reversed lines
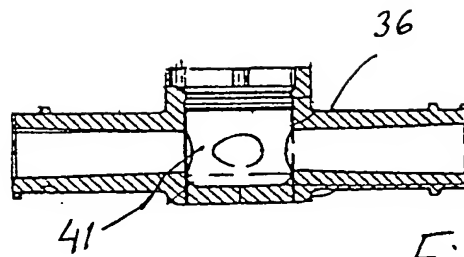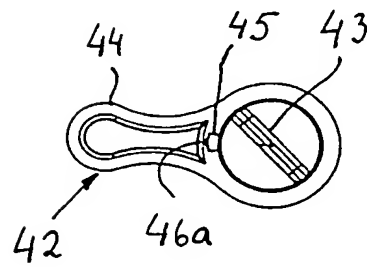

Treatment time (min)
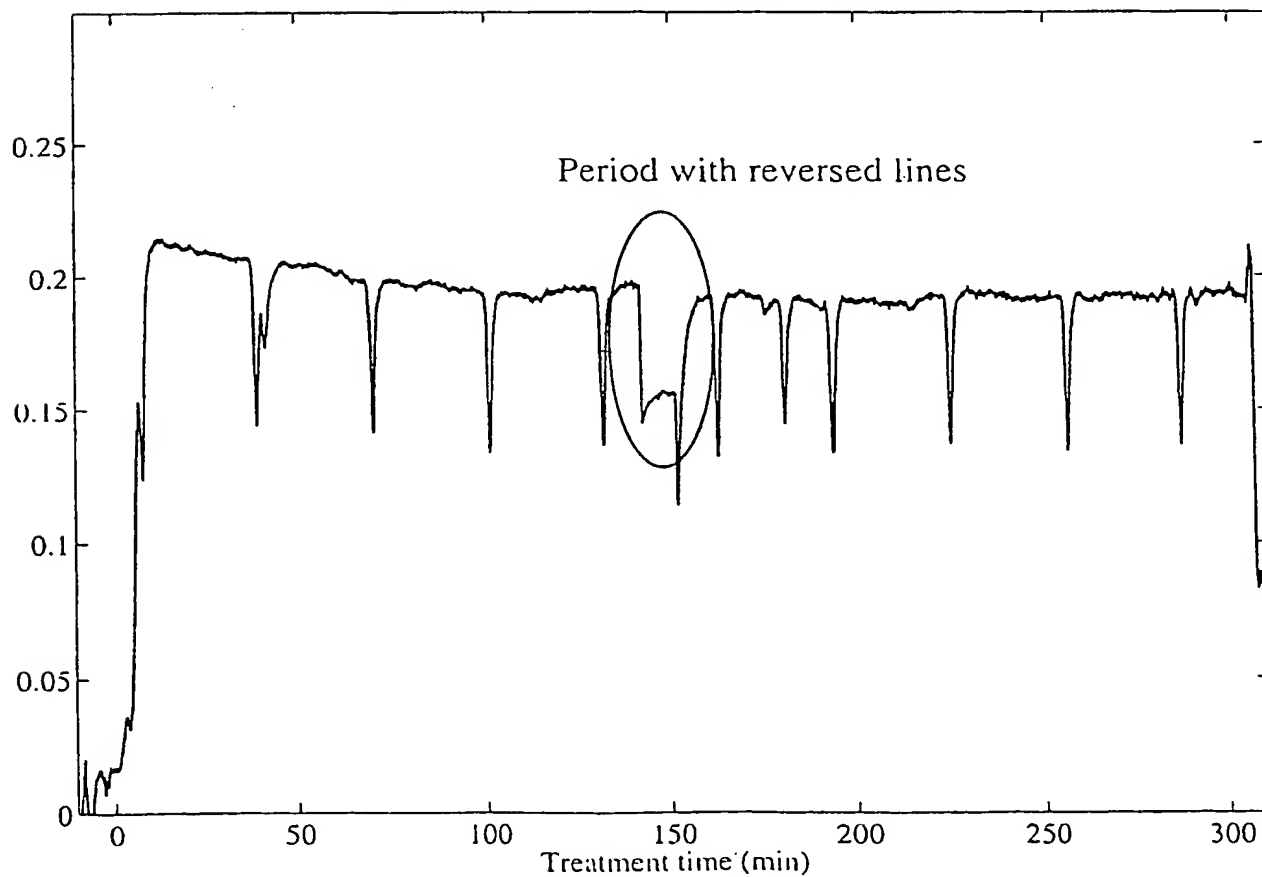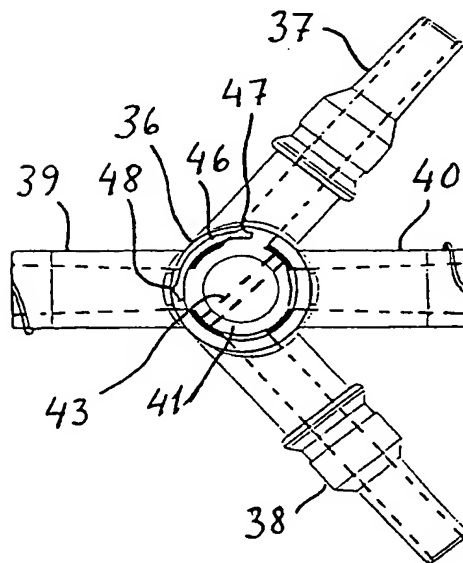
Fig. 12

Fig. 13

Fig. 14

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 99/01915

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61M 1/36, A61B 5/026, G01F 9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61M, G01F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	Advances in renal replacement therapy, Volume 6, No 3, 1999, Sternby J, "Urea sensors - A world of possibilities", page 265 - page 272, see page 271	1-28
P,A	Advances in Renal Replacement Therapy, Volume 6, No 3, 1999, Lindsay RM et al, "Monitoring vascular access flow" page 273 - page 277	1
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[X] Further documents are listed in the continuation of Box C.   [X] See patent family annex.

*	Special categories of cited documents:
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"O"	document referring to an oral disclosure, use, exhibition or other means
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"X"	document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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"&"	document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 February 2000	2 2 -02- 2000

Name and mailing address of the ISA/	Authorized officer
Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. + 46 8 666 02 86	Monika Bohlin/EÖ Telephone No. + 46 8 782 25 00

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 99/01915

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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A	EP 0773035 A2 (FRESENIUS AG), 14 May 1997 (14.05.97), page 2, line 43 - page 3, line 47; page 5, line 15 - page 6, line 21, abstract	1-28
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Information on patent family members

| 02/12/99 | International application No. PCT/SE 99/01915 |

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